UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/568,762	08/10/2006	Stefan Golz	004974.01103	4836

22907 7590 07/09/2008

BANNER & WITCOFF, LTD.
1100 13th STREET, N.W.
SUITE 1200
WASHINGTON, DC 20005-4051

EXAMINER	
SWOPE, SHERIDAN	
ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
07/09/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/568,762	GOLZ ET AL.	
	Examiner	Art Unit	
	/SHERIDAN SWOPE/	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3 and 27-38* is/are pending in the application.

4a) Of the above claim(s) *27,28,33 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,29-32 and 35-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0206;0806*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election, without traverse, of Invention I and sub-invention (D), in their response of April 23, 2008 is acknowledged. The invention elected by said response was directed to an in vitro method for screening for therapeutic agents that modulate KLK8 activity. It is acknowledged that Claims 1, 4-18, and 21-23 have been cancelled, Claims 2 and 3 have been amended, and Claims 27-38 have been added. Since the elected claims, as amended, recite an in vivo assay, the Examiner contacted Applicants' representative, Lisa Hemmendinger, on June 16, 2008 to clarify the elected invention. The Examiner was informed that the elected invention is to be directed to a method of screening in vitro, followed by screening in vivo. Claims 2, 3, and 27-38 are pending. Claims 27, 28, 33, and 34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 2, 3, 29-32, and 35-38 are hereby examined.

Priority

The priority date granted for the instant invention is August 30, 2003, the filing date of EPO 03019799.0, which disclosed the elected invention.

Information Disclosure Statement

A reference of the Information Disclosure Statement filed February 21, 2006, as indicated by strike-out, fails to comply with 37 CFR 1.98(a)(1), which requires that all citation be identified by Author. In addition said reference has not been filed; if Applicants wish for the reference to be considered, it should be filed.

The Information Disclosure Statement filed August 10, 2006 is a duplicate of the Information Disclosure Statement filed February 21, 2006.

Abstract

The abstract is objected to because it is too long.

MPEP 608.01(b) states

> The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Utility

Claims 2, 3, 29-32 and 35-38 are rejected under 35 U.S.C. 101 because the claimed recitation of a method, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 4, 29-32, and 35-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons.

For Claims 2 and 3, the phrase "in a mammal" renders the claims indefinite. It is unclear whether said phrase refers to all recited diseases or only reproductive disorders. The skilled artisan would not know the metes and bounds of the recited invention. Claims 29-32 and 35-38, as dependent from Claim 2 or 3, are indefinite for the same reason. For purposes of examination, it is assumed that "in a mammal" refers to all recited diseases.

For Claims 2 and 3, the phrases "a first activity" and "a second activity" render the claims indefinite. It is unclear whether said phrases mean that (i) two different assays, measuring two different activities, are performed or (ii) a single assay, measuring a single activity, in the presence or absence of the test compound/regulator is performed. The skilled artisan would not know the metes and bounds of the recited invention. Claims 29-32 and 35-38, as dependent from Claim 2 or 3, are indefinite for the same reason. For purposes of examination, it is assumed that the phrases "a first activity" and "a second activity" mean (ii).

For Claims 2(ii) and 3(ii), the phrase "activity of said [KLK8] polypeptide" renders the claims indefinite. It is unclear which activity(s) of the genus of encompassed KLK8 polypeptides is recited. The skilled artisan would not know the metes and bounds of the recited invention. Claims 29-32 and 35-38, as dependent from Claim 2 or 3, are indefinite for the same reason. For purposes of examination, it is assumed that the phrase "activity of said [KLK8] polypeptide" means protease activity.

Claims 2 and 3 provides for the use of a KLK8 polypeptide for identifying therapeutic agent in an in vitro assay, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this

use is actually practiced. Claims 29-32 and 35-38, as dependent from Claim 2 or 3, are indefinite for the same reason.

Claims 2 and 3 provides for the use of a KLK8 polypeptide for identifying therapeutic agent in an in vivo assay, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. Claims 29-32 and 35-38, as dependent from Claim 2 or 3, are indefinite for the same reason.

For Claim 3(ii) and (iii), the phrase "a KLK8 polypeptide" renders the claim indefinite. It is unclear whether said phrases mean to refer back to the KLK8 polypeptide of (i) or a different KLK8 polypeptide. The skilled artisan would not know the metes and bounds of the recited invention. Claims 35-38, as dependent from Claim 3, are indefinite for the same reason. For purposes of examination, it is assumed that the phrases "a KLK8 polypeptide" in (ii) and (iii) refer back to the KLK8 polypeptide of (i).

For Claim 3, the phrase "known regulator" renders the claim indefinite. What is known at one point in time is different from what is known at another point in time. The skilled artisan would not know the metes and bounds of the recited invention. Claims 35-38, as dependent from Claim 3, are indefinite for the same reason.

Claims 2, 30-32, and 36-38 are rendered indefinite for improper antecedent usage as follows.

For Claim 2(ii), the phrase "said polypeptide" should be corrected to "said KLK8 polypeptide".

For Claims 30, 32, 36, and 38, the phrase "the polypeptide" should be corrected to "the KLK8 polypeptide".

For Claims 31 and 37, the phrase "the compound" should be corrected to "the test compound".

Examiner's note: On pages 10-11, the specification defines the term "KLK8" as follows.

--A "KLK8 polynucleotide", within the meaning of the invention, shall be understood as being a nucleic acid molecule selected from a group consisting of (i) nucleic acid molecules encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, (ii) nucleic acid molecules comprising the sequence of SEQ ID NO: 1, (iii) nucleic acid molecules having the sequence of SEQ ID NO: 1, (iv) nucleic acid molecules the complementary strand of which hybridizes under stringent conditions to a nucleic acid molecule of (i), (ii), or (iii); and (v) nucleic acid molecules the sequence of which differs from the sequence of a nucleic acid molecule of (iii) due to the degeneracy of the genetic code; wherein the polypeptide encoded by said nucleic acid molecule has KLK8 activity.

A "KLK8 polypeptide", within the meaning of the invention, shall be understood as being a polypeptide selected from a group consisting of (i) polypeptides having the sequence of SEQ ID NO: 2, (ii) polypeptides comprising the sequence of SEQ ID NO: 2, (iii) polypeptides encoded by KLK8 polynucleotides; and (iv) polypeptides which show at least 99%, 98%, 95%, 90%, or 80% homology with a polypeptide of (i), (ii), or (iii); wherein said polypeptide has KLK8 activity.—

The polypeptide of SEQ ID NO: 2 is the human KLK8 protein taught by Yoshida et al, 1998.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 3, 29-32, and 35-38 are rejected under 35 U.S.C. 112, first paragraph for lack of enablement. The art is enabling for the method rendered obvious by the combination of Sampaio et al, 1996, Yoshida et al, 1998, Colman et al, 1999, Shimizu et al, 1998, and Piesecki et al, 1993, as described below under 35 USC 103(a). However, the specification does not reasonably provide enablement for any method for screening for therapeutic agents by identifying

modulators human KLK8 protease or variants thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In regards to this enablement rejection, the application disclosure and claims are compared per the factors indicated in the decision In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of a comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Claims 3, 29-32, and 35-38 are so broad as to encompass any method for screening for therapeutic agents by identifying modulators human KLK8 or variants thereof. The scope of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of methods broadly encompassed by the claim.

The specific reagents and steps used for identifying a modulator of any enzyme determine the method's success. Likewise, the specific reagents and steps used for identifying a therapeutic agent determine the method's success. Predictability of which steps and reagents can be used to identify the desired modulators requires a knowledge of, and guidance with regard to how said steps and reagents relate to the desired analysis of KLK8 activity. Moreover,

predictability of which steps and reagents can be used to identify the desired therapeutic agents requires a knowledge of, and guidance with regard to how said steps and reagents, including any KLK8 protein, relate to the disease to be treated. In the instant case, the disclosure fails to enable the skilled artisan to identify any therapeutic agent useful for any disease.

It is acknowledged that recombinant and mutagenesis techniques for making variant KLK8 polypeptides, methods for testing compounds for modulation of KLK8 protease activity, and methods for testing compounds as therapeutic agents for many diseases are known. However, it is not routine in the art to screen for the effect of multiple substitutions or multiple modifications of SEQ ID NO: 2 on the protease activity, test the extremely large number of active variants for modulation by any test compound, and then test the compounds for an effect in vivo, as encompassed by the instant claims. Furthermore, the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable (Galye et al, 1993; Whisstock et al, 2003). In addition, how any successful method may, or may not, be altered and still be useful for identifying modulators of any KLK8 variant or therapeutic agent is also unpredictable. Most importantly, neither the specification nor the art provide evidence that KLK8 is the cause or curative agent in any specific disease. No biologically relevant substrates, biochemical or cellular pathways, or specific diseases caused or cured by KLK8 have been disclosed by either the specification or the prior art (Borgono et al, 2004; Pampalakis et al, 2007). Mere assertion that modulators of KLK8 can be used to treat any one of a laundry list of diseases or conditions does not provide the skilled artisan sufficient guidance to treat any specific disease.

The specification does not support the broad scope of Claims 3, 29-32, and 35-38, which encompasses all methods for screening for therapeutic agents by identifying modulators human KLK8 or variants thereof. The specification does not support the broad scope of Claims 3, 29-32, and 35-38 because the specification does not establish: (A) regions of the protein structure which may be modified without affecting the KLK8 protease activity; (B) the general tolerance of the KLK8 protease activity to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired protease activity; (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices of KLK8 variants is likely to have protease activity; (E) the steps and reagents that can be successfully use to identify KLK8 modulators that are therapeutic agents; (F) how to interpret the results of any method for identifying therapeutic agents, i.e. would a useful therapeutic agent be an inhibitor or activator of KLK8 protease activity; (G) any disease or condition that can be successfully treated by an inhibitor or activator of KLK8 protease activity; (H) the specification provides insufficient guidance as to which of the essentially infinite possible disease and conditions encompassed by the generic terms "cardiovascular diseases", "dermatological diseases", "neurological diseases", "metabolic diseases", "cancer disorders", "urological diseases", "gastroenterological diseases" and "reproduction disorders" is likely to be successfully treated with a KLK8 modulator.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of methods for identifying therapeutic agents for an extremely large number of disease and conditions my identifying modulators of a large number

of KLK8 proteins having any or no activity. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Written Description

Claims 3, 29-32, and 35-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 3, 29-32, and 35-38 are directed to a genus of methods for screening for therapeutic agents by identifying modulators of human KLK8 or variants thereof and then testing said modulators in vivo. The specification teaches no such methods. Given this lack of description of representative species encompassed by the genera of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 3, 29, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sampaio et al, 1996 in view of Yoshida et al, 1998 and further in view of Colman et al, 1999 and Shimizu et al, 1998. Sampaio et al teach screening for agents that modulate human plasma kallikrein activity (Table 1). Sampaio et al does not teach screening for agents that modulate human kallikrein8 activity. Yoshida et al teach the sequence of a human kallikrein protein that, based on homology to mouse kallikrein8 is, more likely than not, human kallikrein8 (Fig 2B; section 3.2). It would have been obvious to a person of ordinary skill in the art to determine whether the inhibitors of human plasma kallikrein also inhibit human kallikrein8. Motivation to do so is derived from the desire to determine whether the inhibitors of human plasma kallikrein are specific for that protease, since human plasma kallikrein is a known mediator of arthritis and inflammatory bowel disease (Colman et al; Table 1). It would also be obvious to the skilled artisan to, as a control, to include a kallikrein8 inhibitor in the experiment in order to demonstrate the ability of kallikrein8 to be inhibited under the conditions used. The expectation of success is high, as cell-free methods for identifying modulators of both human plasma kallikrein (Sampaio et al) and human kallikrein8 (Shimizu et al; Table II) are known in the art. The skilled artisan would be further motivated to test any specific plasma kallikrein inhibitor on arthritis and/or inflammatory bowel disease in vivo using the methods taught by Colman et al. Therefore, Claims 2, 3, 29, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sampaio et al, 1996 in view of Yoshida et al, 1998 and further in view of Colman et al, 1999 and Shimizu et al, 1998.

Claims 30, 31, 36, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Sampaio et al, 1996, Yoshida et al, 1998, Colman et al, 1999, and Shimizu et

al, 1998 in view of Piesecki et al, 1993. The teachings of Sampaio et al, Yoshida et al, Colman et al, and Shimizu et al are described above. Said combination does not teach a method using a labeled KLK8 protein or a labeled test compound. However, the use of labeled molecules was well-known in the art. For example, Piesecki et al teach the making of His6-tag labeled proteins which can be used for essentially any purpose, including enzyme assays. It would have been obvious to a person of ordinary skill in the art to use the method of Piesecki et al to prepare His6-tagged KLK8 protein and/or His6-tagged test compounds to be used in the method rendered obvious by the combination of Sampaio et al, Yoshida et al, Colman et al, and Shimizu et al. Motivation to do so derives from the ease in purification of the His6-tag labeled proteins. The expectation of success is high, as the making and using of His6-tag labeled proteins was well-known in the art. Therefore, Claims 30, 31, 36, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Sampaio et al, 1996, Yoshida et al, 1998, Colman et al, 1999, and Shimizu et al, 1998 in view of Piesecki et al, 1993.

Allowable Subject Matter

No claims are allowable.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages. It is also requested that Applicants put the serial number on every page of their response.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Nashed can be reached on 571-272-092834. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SHERIDAN SWOPE/
Primary Examiner, Art Unit 1652